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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/127,738	08/03/98	PONCE DE LEON	F	002076-005

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	9

DATE MAILED: 08/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/127,738	Ponce D Leon et al
Examiner	**Group Art Unit**
Stroup, Carri	1633

☒ Responsive to communication(s) filed on *May 27, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-24* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☒ Claim(s) *24* is/are allowed.

☒ Claim(s) *1-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment Paper 8, filed 5/27/00, has been entered. Claims 1 and 14 have been amended. Claim 24 has been allowed. Claims 1-23 are currently pending in the present application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 5, 13, 16, 18, 19, and 22 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's arguments filed 5/27/00 have been fully considered but they are not persuasive.

It is maintained that the specification fails to provide an enabling disclosure for a method of culturing avian PGC or EG cells or an improved method of producing chimeric avians utilizing EG cells which had been transfected or transformed with a desired nucleic acid sequence, such as one which encodes a therapeutic polypeptide (claims 13, 14, 18, 19). The Applicant states in Paper 8, page 7, that "...the goal of the present was not to produce a transgenic or chimeric avian per se as a novel invention. Rather, Applicants' goal was to develop a long term culture system for avian PGCs that would facilitate the production of transgenic and chimeric avians. " The Applicant also states that long term cultures facilitate the isolation of transfected PGCs and EG cells (Paper 8, page 8, para. 2), but the Applicant

does not explicitly state in what manner or by what experimental procedure this would occur, nor is it readily apparent from the reading of the specification. Additionally, the Applicant asserts that an exhibit disclosing the work of Vick and Simkiss, who generated transgenic chimeric avians utilizing the isolation of transfected PCGs in a short culture method did not express a transgene but rather the PGCs were transfected with defective retroviruses. Likewise, Applicants' own work disclosing photographs of EG cells expressing green fluorescence protein transgene, do not disclose the expression of a therapeutic protein such that it may then be isolated and purified. The lack of enablement for the claimed invention is not merely an issue of isolation of transfected PGC's or EG cells, but rather the lack of a disclosure on teachings specific to transfecting said cells, such as the construct design with regulatory sequences per species transfected, which would result in a high enough level of transgene expression within a chimeric avian such that it could be isolated from the avian's eggs, systemic circulations system, or bodily fluids or tissues, by purification methods routine in the art. It is also held that the issue of enablement regarding the method of purifying the said protein is also rendered moot in light of the lack of enablement in expressing a therapeutic protein (claim 19).

It is also maintained that the specification fails to provide an enabling disclosure for the use of turkey PGC's with the claimed invention (claims 5, 16, 22). The Applicant states in Paper 8, page 3, that the citation of Chang et al by the Examiner is not applicable to the claimed invention because Chang et al does not disclose the combination of growth factors without a feeder layer. The Applicant has failed to supply a sufficient scientific explanation for this assertion, such as the correlation between the lack of a feeder layer and the increased ability to extrapolate the results of culturing PGCs or EGs between different avian species. And although the Applicant also asserts that one reading the patent could readily apply the combination of growth factors as claimed to other species absent undue experimentation with the knowledge of the Applicant's success in hand (Paper 8, page 15, para. 1). It is not disputed that one reading the specification would be motivated to attempt to utilize non-chicken PGCs with the claimed culture method, but in light of Chang et al (Paper 6, page 3) and the unpredictability in effectively culturing PGCs such that

they could be utilized in a method of generating chimeric avians, then the Office maintains that it would require undue experimentation to adjust the culture conditions for each species' PGCs cultured.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4, 6-12, 14, 15, 17, 20, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pain et al (1996) in view of Labosky et al (1994), Han et al (12/94) and Godin et al (8/91) .

Applicant's claimed invention is to a method for culturing avian primordial germ cells (PGS's) and germ cells (EG) and their use in an improved method of generating chimeric avians comprising the following steps: isolating primordial germ cells from a desired avian and culturing said cells in a culture medium containing at least the following growth factors: leukemia inhibitory factor, basic fibroblast growth factor, stem cell factor, and insulin-like growth factor in amounts sufficient to maintain said PGC's for prolonged periods in tissue culture having a compact multilayer like appearance; and identifying EG cells contained therein. The claimed invention also includes the use of PGCs and EGs which have been transfected with desired nucleic acid sequence, and the use of maximal amounts of growth factors which are 2-100X the minimal amounts.

Pain et al teach the method of culturing avian embryonic stem cells collected from chicken blastoderms at stage X of development, which resulted in a donor derived phenotype thus demonstrating a germ line transmission (pg 2341, col 1, para 4; pg 2344, col 2, para 2-pg 2345, last para.). Culture methods included 10ng/ml bFGF, 20 ng/ml

h-IGF-1, 1% vol/vol avian-SCF, and 1% vol/vol h-LIF; and wherein a combination of aSCF, bFGF, and mLIF strongly enhanced the number of alkaline-phosphatase-positive colonies (pg 2340, col 1, para 1; pg 2341, col 2, para 3; Fig 2, pg 2342), and where upon transfer into avian embryos develop into PGCs. Pain et al also teach that the use of LIF is necessary for the growth and long-term maintenance of ES cells in culture resulting in cells that were ECMA-7, SSEA-1, and EMA-1 positive for at least 35 passages and more than 160 days (pg 2343, Figure 4, and col 2), and successful germline transmission in Barred Rock black strain chickens (pg 2344, col 2, para 2). Lastly, Pain et al also discloses that there was no difference in the effects of culturing avian embryonic cells with growth factors in the absence of presence of a feeder layer (pg 2341, col. 2, para. 4).

Labosky et al teach that murine PGC's cultured in SCF, LIF, and bFGF allows the un-differentation of PGC's into EG cell lines, by a mechanism which has yet to be discovered, and wherein the only difference known to exist between EG's and ES's is the pattern of DNA methylation within region 2 of the Igf2r gene. Labosky et al also teach that both EG's and ES's differentiate in vitro and in vivo, and both EG cells and ES cells can differentiate into functional sperm and thereby transmit their genome through the germline (pg 3201, col 1, para 3).

Han et al teach that various artisans had disclosed methods of culturing PGC's and the transfection of avian PGC's with retroviral vectors such that the PGC's contained a heterologous nucleic acid and the use of such in generating chimeric avians (pg 463-464). Han et al does not teach the use of specific culture conditions, such as the use of SCF, LIF, bFGF, and IGF.

Godin et al disclose that in the culturing of primordial germ cells with SCF in the absence of a feeder cell layer causes a "large increase in the initial survival and apparent motility of PGC in culture". (abstract)

In light of Han, Godin, Pain and Labosky et al, it would have been obvious to one of ordinary skill in the art to culture avian PGC's, such as chicken,in a culture medium comprising 10ng/ml bFGF, 20 ng/ml h-IGF-1, 1% vol/vol avian-SCF, and 1% vol/vol h-LIF with or without a feeder layer. One would be motivated to do this to generate PGC's

that could be maintained in culture long-term for facilitating their use in generating chimeras and to use SCF in the absence of a feeder cell layer to promote the initial survival of PGC's in culture (Godin et al). There would have been a reasonable expectation of success because the same culture medium conducted on chicken ES's resulted in at least 35 passages, 160 day utility, and successful germline transmission, therefore a substitution of EG's for ES's would have been expected to produce the same results (Labosky et al, pg 3201, col 1, para 3). In light of Han et al it would also have been obvious to transfect said cells with a nucleic acid vector and utilize such in a method of generating chimeric avians. It is also noted that the amount of growth factors used are result effective variables which one of ordinary skill in the art could readily ascertain through routine experimentation.

The Applicant states in Paper 8, page 17, that it is unclear as to why it would have been obvious for the skilled artisan to combine the disclosures of Pain and Labosky et al when the cited references pertain to entirely different cell types, wherein Pain et al discloses a method of culturing blastoderm cells wherein a small percentage are PGCs. It is noted that throughout the Pain et al reference assays for the effects of different culture conditions on the embryonic stem cells within is disclosed and in which the authors state that "In an attempt to develop cultures of avian totipotent embryonic cells (potentially ES cells), we started from chicken or quail blastoderms..." (Pg 2341, col 1, para. 4). Labosky et al also teaches the use of the same growth factors (with the exception of IGF) to culture PGC's such that they convert to EG's or ES's. Therefore, it is maintained that in light of Pain and Labosky it would have been obvious to one of ordinary skill in the art to culture avian PGC's in a culture comprising bFGF, IGF, SCF, and LIF with or without a feeder cell layer for the purpose of generating EG's or ES's which may be maintained in culture for long periods of time, (e.g. up to 160 days or 5 months). It is also noted that the claimed composition is not limited to the four growth factors, therefore Applicant's assertion that Pain et al's use of IL-11 renders the reference non-applicable is moot (Paper 8, page 18).

Claim 24 is free of the prior art of record and is allowable because there is no prior record of cell line P102896.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-0294.

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